SARS-CoV-2 Episode 2? A sequel nobody wants to see

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Reports of reinfection with SARS-CoV-2 suggest that the immune response to primary infection may have insufficient duration and/or breadth, at least in some individuals. Taken together with evidence that immunity to seasonal coronaviruses often wanes within a year[1, 2], these reports raise concern about the long-term effectiveness of SARS-CoV-2 vaccines. While case reports of SARS-CoV-2 reinfection have been increasingly reported since August 2020[3], few studies to date have attempted to characterize its frequency more broadly.

In this issue of *Clinical Infectious Diseases*, Lee *at al.* report results from a detailed evaluation of potential SARS-CoV-2 reinfection cases between May and July 2020[4]. The authors cast a wide net to identify potential reinfections, leveraging the Centers for Disease Control and Prevention and Infectious Disease Society of America's provider-based surveillance system, Emerging Infections Network, to request case referrals. Cases were evaluated using an exhaustive combination of clinical and laboratory parameters, and ultimately the authors did not confirm any cases of reinfection within 90 days after primary infection. These results are in agreement with other studies demonstrating low rates of reinfection at the population level[5, 6], and the rigorous study by Lee *et al.* emphasizes several key points.

One important message highlighted by the authors is that identifying SARS-CoV-2 reinfections is difficult. Lee *et al.* evaluated nearly 300 submitted cases, performed detailed review for 73, and ultimately identified only 19 individuals with the highest suspicion for reinfection. These individuals had a second episode of symptoms compatible with SARS-CoV-2, a repeat positive reverse transcription PCR (RT-PCR) test for SARS-CoV-2, and no alternative diagnosis. In addition, many individuals had plausible re-exposure to SARS-CoV-2, despite it being early in the pandemic, because 68% of them were healthcare workers. The authors selected this subset of the 19 highest-suspicion reinfection cases from a wide starting pool, underscoring the need for time, effort, and expertise in evaluating potential cases.

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Conclusive evidence for reinfection requires identification of distinct SARS-CoV-2 variants between the first and second episodes, as determined by comparative viral genome sequencing[7]. This in turn depends upon the availability of paired samples, with sufficient amounts of SARS-CoV-2 RNA to allow genome sequencing. In the present study, paired samples were only available from 6 of the 19 highest-suspicion individuals, and in all cases, there was insufficient viral RNA to allow genome sequencing from the samples obtained during the second episode.

What could explain the low levels of SARS-CoV-2 RNA at the time of the second episode? The authors note that samples were collected within three days of symptom onset, when the viral load would be expected to be near peak, at least in primary infection[8, 9]. Because viral loads generally decline over time, and RNA can persist for weeks to months after primary infection[8, 10], it is reasonable to conclude that many of these individuals had lingering RNA from their primary infections 1-2 months prior, rather than reinfection.

A possible alternative explanation is that some of these individuals (who had symptoms, no alternative diagnosis, and plausible exposure) did experience reinfection, but it was accompanied by partial immune protection, which lowered the viral burden. Partial immunity has been described for individuals experimentally reinfected with seasonal coronaviruses[11], as well as in a ferret model of SARS-CoV-2, in which pre-existing antibodies did not prevent reinfection but did lead to lower viral loads and more rapid clearance[12]. Individuals with existing antibodies to SARS-CoV-2 from primary infection have experienced reinfection (although rarely), but this does not seem to be consistently associated with lower viral RNA levels[5, 6, 13, 14]. Enhanced methods are needed to distinguish between RNA persistence from primary infection and reinfection when viral RNA levels are low.

In the present study, reinfection may also have occurred in some of the 24 asymptomatic individuals described, 12 of whom could also be considered high-suspicion cases, because they had two negative intervening RT-PCR tests and plausible risk for re-exposure (residing in long-term care facilities). Viral RNA levels were unknown for most of

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the asymptomatic individuals, and paired samples were not received, leading the authors to conclude that reinfection could not be ruled out. This is an important consideration because a number of cases of SARS-CoV-2 reinfection have been described in asymptomatic individuals[6, 15].

Overall, the detailed study by Lee *et al.* provides reassurance that SARS-CoV-2 reinfection is uncommon within 90 days after initial infection, and if present, is unlikely to be associated with symptoms and high viral load. The authors appropriately emphasize the importance of assessing the risk of reinfection more than 90 days after initial infection, when immunity may[16, 17] or may not[18, 19] have waned. Recent studies suggest that reinfection more than 90 days after initial infection is also uncommon, based on studies among high-exposure healthcare workers[5, 6] and residents of care facilities[20].

Despite reassuring results from this and other studies, continued surveillance for SARS-CoV-2 reinfection is essential for several reasons. First, the opportunity for reinfection increases substantially as the number of primary SARS-CoV-2 infections increases. In addition, surveillance for reinfection complements the necessary monitoring for and investigation of post-vaccine infections. Finally, the landscape of reinfection and post-vaccine infection may be substantially altered by the emergence of SARS-CoV-2 variants with properties that allow immune evasion. For example, viruses containing the spike protein mutation E484K are not neutralized as easily as wild type viruses by convalescent sera[21] or sera from vaccinated individuals[22]. Reinfection has already been reported with E484K-containing variants B.1.351[23], P.2[24], and P.1[25], as well as variant B.1.1.7[26], which does not contain E484K. In all of these cases, the first and second infections were more than 90 days apart, underscoring the complex and potentially synergistic roles of immune evasion and waning immunity. Ongoing surveillance for reinfection and post-vaccine infection at both the provider level and the population level will be instrumental in guiding our response to the SARS-CoV-2 pandemic.

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References

1. Galanti M, Shaman J. Direct Observation of Repeated Infections With Endemic Coronaviruses. J Infect Dis **2021**; 223(3): 409-15.
2. Edridge AWD, Kaczorowska J, Hoste ACR, et al. Seasonal coronavirus protective immunity is short-lasting. Nat Med **2020**; 26(11): 1691-3.
3. To KK, Hung IF, Ip JD, et al. COVID-19 re-infection by a phylogenetically distinct SARS-coronavirus-2 strain confirmed by whole genome sequencing. Clin Infect Dis **2020**.
4. Lee JT, Hesse EM, Paulin HN, et al. Clinical and Laboratory Findings in Patients with Potential SARS-CoV-2 Reinfection, May-July 2020. Clin Infect Dis **2021**.
5. Dimeglio C, Herin F, Miedouge M, Martin-Blondel G, Soulat JM, Izopet J. Protection of healthcare workers against SARS-CoV-2 reinfection. Clin Infect Dis **2021**.
6. Lumley SF, O'Donnell D, Stoesser NE, et al. Antibody Status and Incidence of SARS-CoV-2 Infection in Health Care Workers. N Engl J Med **2021**; 384(6): 533-40.
7. CDC. Common Investigation Protocol for Investigating Suspected SARS-CoV-2 Reinfection. Available at: https://www.cdc.gov/coronavirus/2019-ncov/php/reinfection.html. Accessed 2/27/2021.
8. Wolfel R, Corman VM, Guggemos W, et al. Virological assessment of hospitalized patients with COVID-2019. Nature **2020**; 581(7809): 465-9.
9. To KK-W, Tsang OT-Y, Leung W-S, et al. Temporal profiles of viral load in posterior oropharyngeal saliva samples and serum antibody responses during infection by SARS-CoV-2: an observational cohort study. The Lancet Infectious Diseases **2020**; 20(5): 565-74.
10. Vibholm LK, Nielsen SS, Pahus MH, et al. SARS-CoV-2 persistence is associated with antigen-specific CD8 T-cell responses. EBioMedicine **2021**; 64: 103230.
11. Reed SE. The behaviour of recent isolates of human respiratory coronavirus in vitro and in volunteers: evidence of heterogeneity among 229E-related strains. J Med Virol **1984**; 13(2): 179-92.

Accepted Manuscript

12. Kim YI, Kim SM, Park SJ, et al. Critical role of neutralizing antibody for SARS-CoV-2 reinfection and transmission. Emerg Microbes Infect **2021**; 10(1): 152-60.
13. Prado-Vivar B, Becerra-Wong M, Guadalupe JJ, et al. A case of SARS-CoV-2 reinfection in Ecuador. The Lancet Infectious Diseases **2020**.
14. Selhorst P, Van Ierssel S, Michiels J, et al. Symptomatic SARS-CoV-2 reinfection of a health care worker in a Belgian nosocomial outbreak despite primary neutralizing antibody response. Clin Infect Dis **2020**.
15. Abu-Raddad LJ, Chemaitelly H, Malek JA, et al. Assessment of the risk of SARS-CoV-2 reinfection in an intense re-exposure setting. Clin Infect Dis **2020**.
16. Ibarrondo FJ, Fulcher JA, Goodman-Meza D, et al. Rapid Decay of Anti-SARS-CoV-2 Antibodies in Persons with Mild Covid-19. N Engl J Med **2020**; 383(11): 1085-7.
17. Marot S, Malet I, Leducq V, et al. Rapid decline of neutralizing antibodies against SARS-CoV-2 among infected healthcare workers. Nat Commun **2021**; 12(1): 844.
18. Dan JM, Mateus J, Kato Y, et al. Immunological memory to SARS-CoV-2 assessed for up to eight months after infection. bioRxiv **2020**.
19. Gudbjartsson DF, Norddahl GL, Melsted P, et al. Humoral Immune Response to SARS-CoV-2 in Iceland. N Engl J Med **2020**; 383(18): 1724-34.
20. Jeffery-Smith A, Iyanger N, Williams SV, et al. Antibodies to SARS-CoV-2 protect against re-infection during outbreaks in care homes, September and October 2020. Euro Surveill **2021**; 26(5).
21. Greaney AJ, Loes AN, Crawford KHD, et al. Comprehensive mapping of mutations in the SARS-CoV-2 receptor-binding domain that affect recognition by polyclonal human plasma antibodies. Cell Host Microbe **2021**.
22. Xie X, Liu Y, Liu J, et al. Neutralization of SARS-CoV-2 spike 69/70 deletion, E484K and N501Y variants by BNT162b2 vaccine-elicited sera. Nat Med **2021**.
23. Zucman N, Uhel F, Descamps D, Roux D, Ricard JD. Severe reinfection with South African SARS-CoV-2 variant 501Y.V2: A case report. Clin Infect Dis **2021**.

Accepted Manuscript

24. Nonaka CKV, Franco MM, Graf T, et al. Genomic Evidence of SARS-CoV-2 Reinfection Involving E484K Spike Mutation, Brazil. Emerg Infect Dis **2021**; 27(5).

25. Naveca F. SARS-CoV-2 reinfection by the new Variant of Concern (VOC) P.1 in Amazonas, Brazil. Available at: https://virological.org/t/sars-cov-2-reinfection-by-the-new-variant-of-concern-voc-p-1-in-amazonas-brazil/596. Accessed 2/27/21.

26. Harrington D, Kele B, Pereira S, et al. Confirmed Reinfection with SARS-CoV-2 Variant VOC-202012/01. Clin Infect Dis **2021**.

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